

CERTIFICATE OF ELECTRONIC FILING

January 5, 2007

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Didier Trono
Patrick Salmon

Serial No.: 10/010,081

Filed: November 9, 2001

For: METHODS AND COMPOSITIONS
RELATING TO IMPROVED
LENTIVIRAL VECTORS AND THEIR
APPLICATIONS

Group Art Unit: 1633

Examiner: Kaushal, Sumesh

Atty. Dkt. No.: CLFR:010US

REPLY BRIEF

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Commissioner:

Applicants hereby submit their Reply Brief in reply to the Examiner's Answer mailed November 14, 2006, which brings the due date to January 14, 2007.

It is believed that no fees are due; however, if any such fees are due, the Commissioner is authorized to deduct any such fees from Fulbright & Jaworski LLP deposit account 50-1212/CLFR:010US.

Appellants respond to the Examiner's arguments as follows:

A. *Whether the subject matter of claims 4-5, 7-8, 12, 25, 30-34 and 38-45 is obvious over the combination of Zufferey I in view of Deisseroth.*

In response to the Examiner's arguments, Appellants first note that the claims require 1) lentiviral transduction of *hematopoietic progenitor* ("stem") cells, 2) using a "*self-inactivating*" SIN lentiviral vector, 3) carrying a transgene under the control of a *promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200*, 4) in *both* the hematopoietic progenitor cell *and* in a differentiated hematopoietic cell. We contend that no *prima facie* case of obviousness has been set forth.

The Examiner concedes that Zufferey I fails to teach or suggest lentiviral transduction of a hematopoietic progenitor cell, its disclosure being limited to transduction of differentiated cells such as human peripheral blood lymphocytes ("PBLs"; Answer at page 5, first full paragraph). The primary promoter taught by Zufferey I is the CMV promoter. However, as Appellants explained in their opening brief, the CMV promoter *fails* to promote detectable expression at a signal-to-noise ratio of between 10 and 200 in hematopoietic progenitor cells (HPCs). Brief at page 9. Thus, even if one were motivated to extend the teachings of Zufferey I to use the Zufferey I construct in HPCs, which we contest, such a combination would still fail to meet the limitations of the claims.

The Examiner argues that Zufferey I demonstrates that its CMV vector is capable of promoting high levels of expression, and refers to Table 2, page 9876. Answer, top of page 5. This argument misses the point – Appellants fully agree that the CMV promoter works well in differentiated cells such as PBLs. However, the claims require the use of a promoter that promotes high levels of expression in both progenitor cells and in differentiated cells. Our

specification demonstrates convincingly that the CMV promoter does *not* meet this requirement. Brief at page 9.

Deisseroth is cited as providing the motivation to use the Zufferey I CMV construct to transduce hematopoietic progenitor cells. However, as we have shown, such a combination would not achieve the subject matter of the claims in that the CMV promoter is incapable of promoting detectable expression at a signal-to-noise ratio of between 10 and 200 in hematopoietic progenitor cells.

The Examiner's response to the foregoing is that "the instant claims is [sic, are] not limited to a particular structure and especially to a particular internal promoter" and that "the 'signal to noise ration' is merely an 'arbitrary value'". Answer at bottom of page 10. Both of these positions are without merit. First, there is defining a structure by means of a functional limitation is not at all improper,¹ and, here, the functional description serves to identify and distinguish the claimed promoters – and, indeed, serves to exclude the use of promoters such as the CMV promoter. Secondly, there is nothing "arbitrary" about the 10 to 200 range – this is the range that permits ready detection of expression and defines that range believed to be useful in the practice of the invention:

The viral vectors of the present invention will also include an expression cassette comprising a transgene positioned under the control of a promoter that is active to promote detectable transcription of the transgene in a human hematopoietic progenitor cell. To determine whether a particular promoter is useful, a selected promoter is tested in the construct *in vitro* in a selected progenitor cell and, if the promoter is capable of promoting expression of the transgene at a detectable signal-to-noise ratio, it will generally be useful in accordance with the present invention. A desirable signal-to-noise ratio is one between about 10 and about 200, a more desirable signal-to-noise ratio is one 40 and about 200, and an even more desirable signal-to-noise ratio is one between about 150 and about 200. One means of testing such a promoter, described in more detail hereinbelow, is

¹ We note, for example, that no concerns under 35 U.S.C. §112, first or second paragraphs, have been raised.

through the use of a signal generating transgene such as the green fluorescent protein (GFP).

Specification, page 6, lines 1-12.

The Case reference is relied upon by the Examiner as purportedly teaching that the CMV promoter does promote expression within the claimed 10 to 200 ratio range in hematopoietic progenitor cells. Answer at paragraph bridging pages 11 and 12. First, we disagree with the premise that Case teaches a level of expression that meets this limitation as there is no data in this reference that would permit one to draw such a conclusion. However, Case is not relevant for a much more basic reason: the studies described in Case using the CMV lentivirus do not involve the use of a “self-inactivating” SIN lentivirus. One of the problems that the present invention seeks to address is how to prepare and SIN lentivirus that is capable of high level expression, since SIN vectors have as a notorious problem the inability to achieve high level expression, particularly in hematopoietic progenitor cells. Specification, last paragraph of Background and first paragraph of Summary, pages 3-4. Thus, Case actually teaches away from the invention by suggesting that the CMV promoter is effective when, at least in the context of SIN vectors, it is not. We know from our own experimental evidence that the CMV promoter, in the context of an SIN vector, is only minimally active in most progenitor cells. This is shown most dramatically in the studies depicted in Fig. 1, where it can be seen that the CMV promoter driven expression is virtually undetectable in CD34+ cells. Case, on the other hand, demonstrates that CMV apparently provides detectable expression when used in the context of a non-SIN vector – thus, the Case actually teaches away from the invention by suggesting that CMV is a promoter of choice in HPCs when, in fact, it is not if one is using an SIN vector. By way of theory, we suspect that the reason the CMV promoter works in the context of non-SIN

lentivectors is that the CMV promoter might be boosted by the enhancer element present in the wild type HIV LTR, which enhancer is deleted in the SIN vector.

Claims 38 and 39-45

Claim 38 is still further removed, in that it requires incubation of the lentiviral-transduced stem cell in a differentiation medium. The Examiner relies on Deisseroth at page 1608, para. 1, lines 3-5, for the proposition that incubation of HPCs in certain medium induces maturation. However, a careful reading of this excerpt from Deisseroth shows just the opposite!:

(a) Ex vivo serum-free culture conditions that support the survival and self renewal of stem cells have been developed (14, 15), which will enable future trials to avoid the conditions used for transduction in the early MDR-1 trials (incubation in serum containing medium supplemented with late-acting growth factors, such as interleukin-3, in the presence of SCF), which have been shown to induce maturation of stem cells and to, therefore, reduce their self renewal potential in transplantation settings

Deisseroth, page 1608, paragraph bridging columns 1 and 2 (emphasis ours). This excerpt shows that Deisseroth actually teaches that it is undesirable to permit hematopoietic progenitor cells to differentiate (...will **enable** future trials to **avoid** the conditions used for transduction ... which have been shown to induce maturation of stem cells ..."; emphasis ours). Note that the "trials" being referred to were not trials employing lentiviral vectors and thus there can be no inherent anticipation, and since this excerpt states that it is undesirable to permit the HPCs to mature, the combination of Deisseroth with Zufferey I would **teach away** from placing lentiviral transduced HPCs into culture medium that would permit maturation.

Similar arguments apply with respect to dependent claims 39-45, which are still further removed from the art in that they specify differentiation into distinct differentiated cell types such as erythroid cells, granulocytes, monocytes or dendritic cells. The Examiner attempts to

cite Case (which is curiously not formally cited in the rejection) for the proposition that Case teaches or suggests such differentiation. The Examiner refers us to page 2989, col. 2, para. 3-6 and page 2992, col. 1, para. 3, in support of this allegation. However, we have reviewed these excerpts and have been unable to identify what the Examiner believes is relevant. All that these excerpts show is that the authors were able to stably transduce HPCs in long term culture – while it is shown that the transduced HPCs are able to divide, they are shown to maintain their HPC phenotype (i.e., maintain CD34 expression). Indeed, this is the overall goal of this study, as expressed in the last sentence of the Background section, where it is stated that “we show that lentiviral vectors are able to provide efficient, stable transduction in primitive, quiescent human progenitors normally resistant to transduction with MLV.” Case, page 2988, col. 1.

B. Whether the subject matter of claims 7-10 is obvious over the combination of Zufferey I and Deisseroth, as above, further in view of Chang et al. (exhibit 3, appendix ix; hereinafter “Chang”).

With respect to claims 7-10, the Examiner includes a further reference to Chang.

First, in that claims 7-10 depend from independent claim 30 (addressed in connection with the preceding rejection), such claims are patentable for the same reasons discussed in the preceding section.

The Examiner’s principal argument is that one of skill would be motivated to employ the SIN vectors of Zufferey to transduce the hematopoietic progenitor cells as taught by Chang, and that it would be expected that such a combination would provide the high expression levels observed by Chang for non-SIN lentivectors (referring to Figure 5 of Chang). We disagree.

Zufferey, which admittedly fails to disclose HPC transduction, very clearly teaches that the ability of the SIN vectors to effect high level expression in any given cell type is *per se* unpredictable. For example, in column 2 of page 9878 Zufferey states that a comparison of

various SIN and full-length HIV vectors revealed promoter- and cell-specific differences in the degree of promoter interference. Thus, Zufferey teaches that the effect of U3 deletion (*i.e.*, as in SIN vectors) on promoter activity is variable depending on the promoter and cell type in question. For example, Table 3 on page 9877 shows that while PGK expression in 293T cells was higher in SIN vectors than in vectors with an intact LTR, U3 deletion had very little effect on PGK activity in HeLa and 3T3 cells. Furthermore, PGK promoter activity was reduced in F208 cells when expressed from a SIN vector as compared to vector with an intact LTR. Similarly, when CMV was used as the internal promoter the effect of U3 deletion on promoter activity was also variable depending on the host cell type. In this case, CMV expression was enhanced in SIN vectors only in 293T cells, while internal promoter (CMV) activity was decreased by U3 deletion in all other cells types tested. Thus, the effect of U3 deletion on the activity an internal promoter be either positive or negative depending on promoter and cell type – in other words, one of skill simply would not have a reasonable expectation that SIN vectors, carrying a given promoter, would express at the specified signal-to-noise ratio. See MPEP 2143.02; *In re Rinehart*, 531 F.2d 1048, 189 U.S.P.Q. 143 (CCPA 1976)

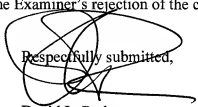
In light of the foregoing, the Board is requested to overturn the Examiner's holding of obviousness of claims 7-10.

C. *Whether the subject matter of claims 19, 22 and 23 is obvious over the combination of Zufferey I and Deisseroth, as above, further in view of Zufferey et al., J. Virol., 1999 (exhibit 4, appendix ix; hereinafter "Zufferey II").*

Appellants will rely on its arguments with respect to the patentability of claim 30 as set forth in the opening brief and in section A. above.

D. Conclusion

In light of the arguments set forth in the opening brief and in the foregoing reply, Appellants request that the Board overturn the Examiner's rejection of the claims.



Respectfully submitted,

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